REMARKS

Claims 6-8 are pending.

Claim Rejections -- 35 U.S.C. 103

Applicants respectfully traverse the obviousness rejections of claims 6-8 over Chang (Acta Pharmacologica Sinica, August 2003, 24: 796-804) in view of Xiong (Yaoxue Xuebao, 2000, 35, pp. 408-412) or and further in view of Izozumi (Tokai J. Exp. Clin. Med., 1998, vol. 23, pp. 103-117).

The Examiner relied on Chang for teaching the use of l-butylphthalide (NBP) to improve ischemia-induced apoptosis. Page 3 of the Office Action alleged that "Chang discloses that the beneficial effects NBP on cerebral ischemia-induced apoptosis might be useful for the treatment of ischemic cerebrovascular diseases." Applicants disagree because Chang does not disclose that the beneficial effects of l-butylphthalide on cerebral ischemia-induced apoptosis might be useful for the treatment of ischemic cerebrovascular diseases. Instead Chang merely concludes that the findings reported in Chang "might have important implications for the study and treatment of ischemic cerebrovascular diseases" (see the last sentence of Chang). The disclosure that l-butylphthalide might have important implications for the treatment of ischemic cerebrovascular diseases is not the same as disclosing "that the beneficial effects NBP on cerebral ischemia-induced apoptosis might be useful for the treatment of ischemic cerebrovascular diseases" because it is not clear what Chang meant with the term "important implications."

In addition, there is no clear relationship between the inhibition of apoptosis caused by l-butylphthalide and the treatment of cerebral infarct. There is also no clear relationship between the inhibition of apoptosis caused by l-butylphthalide and the reduction of the volume of cerebral infarct. The relationship of neuronal apoptosis and infarct size is complicated. Even though Chang et al., J. Biomed. Sci. 2009, 16:9) reported that the change of neuronal apoptosis was correlated to the infarct size, but the person of ordinary skill in the art would not have this report of Chang et al. because Chang et al., J. Biomed. Sci. 2009, 16:9, was published after the effective filing date of the instant patent application. In contrast, Wang et al. demonstrated that TACE inhibitor reduced infarct size neurological deficits, and had no effect on apoptosis measured by levels of active caspase-3 expression and DNA fragmentation (Wang et al., *Inhibition of tumor*

necrosis factor-alpha-converting enzyme by a selective antagonist protects brain from focal ischemic injury in rats, Mol. Pharmacol. 2004; 65(4):890-6, a copy of which was attached to the Supplemental Response filed on June 29, 2009). Thus, to a person of ordinary skill in the art on the effective filing date of the instant patent application, there is no reasonable expectation that L-butylphthalide would reduce the volume of the cerebral infarct, based merely on Chang's disclosure that L-butylphthalide inhibited transient focal cerebral ischemia-induced apoptosis the inhibition of apotosis. At least due to these deficiencies of Chang, the Office Action fails to prove that the claimed invention is prima facie obviousness.

The Office Action concluded that Chang differs from the claimed invention in the use of l-butylphthalide in the therapeutic treatment of cerebral infarction. The Office Action tried to rely on Xiong and Izozumi to cure the deficiency of Chang. However, as explained below, the Office Action's reliance on Xiong and Izozumi to cure the deficiency of Chang failed.

Xiong discloses an *in vivo* study of rats subjected to middle cerebral artery occlusion in page 409. In the *in vivo* study of Xiong, dl-butylphthalide, not l-butylphthalide, was administered intraperitoneally in the rats at a dose of 5 or 10 mg/kg 10 minutes BEFORE the middle cerebral artery occlusion. The pre-treatment of the rats with dl-butylphthalide

(a) prevented the decrease in the mitochondrial membrane fluidity in part of the brain caused by cerebral ischemia induced by middle cerebral artery occlusion; and

(b) improved the severe swelling and marked vacuolation of mitochondria in part of the brain caused by cerebral ischemia induced by middle cerebral artery occlusion.

Xiong discloses that the improving effects of dl-butylphthalide on mitochondrial injury and morphological changes might contribute to its therapeutic action on experimental stroke" (Abstract, last sentence; emphasis added). Applicants note that in the *in vivo* study of Xiong, dl-butylphthalide, not l-butylphthalide, was administered in the rats. In addition, the dl-butylphthalide was administered 10 minutes BEFORE the local ischemica. These differences make it difficult for a person of ordinary skill in the art to determine, based on the results of Xiong's *in vivo* study, whether l-butylphthalide would be reasonably expected to be successful in treating cerebral infarct. Because dl-butylphthalide was administered BEFORE the local ischemia induced by middle cerebral artery occlusion, instead of administered AFTER the development of cerebral infarct, it would be difficult to reasonably predict whether dl-butylphthalide would be effective in treating, instead of protecting against, cerebral infarct.

Because dl-butylphthalide, not l-butylphthalide, was administered, it would be even be more difficult to reasonably predict whether l-butylphthalide would be effective in treating cerebral infarct. In addition, the relationship between the mitochondrial effects detected by Xiong in the *in vivo* study and the reduction in the volume of the cerebral infarct recited in claims 6-8 is unclear. Thus, based on Chang in view of the *in vivo* results of Xiong, the person of ordinary skill in the art would not have any reasonable expectation that l-butylphthalide would be effective in treating cerebral infarct.

Xiong also discloses an *in vitro* study in which a primary culture of fetal rat neurons subjected to hypoxia and hypoglycemia was exposed to l-, d- or dl-butylphthalide at a concentration of 10 μm/L at the same time as the hypoxia and hypoglycemia treatment, and the exposure to l-, d- or dl-butylphthalide prevented the decreases in mitochondrial membrane potential and ATPase. Because the person of ordinary skill in the art would not know what *in vivo* dose is equivalent to an *in vitro* concentration of 0 μm/L and whether an *in vivo* administration of l-butylphthalide would expose the neurons in the brain region at or near the cerebral infarct at the same concentration for the same duration as in the *in vitro* experiments of Xiong, it is difficult to extrapolate from the results of the *in vitro* experiments of Xiong to the *in vivo* treatment scenario. In addition, there is no clear relationship between the changes in the volume of cerebral infarct and the changes in mitochondrial membrane potential and ATPase. Thus, based on Chang in view of the *in vitro* results of Xiong, the person of ordinary skill in the art would not have any reasonable expectation that l-butylphthalide would be effective in treating cerebral infarct.

As a result, there would have been no reasonable expectation based on Chang in view of Xiong that l-butylphthalide would be effective in treating cerebral infarct.

The Office Action merely relies on Izozumi as a supplemental reference to demonstrate the state of the art in using the focal cerebral ischemia model as an experimental model of cerebral infarction. Izozumi does not cure the deficiencies of Chang in view of Xiong discussed above. Therefore, claims 6-8 would not have been obvious over Chang in view of Xiong and Izozumi.

In page 4, the Office Action regards the phrase "to reduce the volume of the cerebral infarct" recited in the claims as merely "the underlying pharmacological mechanism" of the treatment of cerebral infarct with l-butylphthalide. The Office Action takes a position that the

discovery of the pharmacological mechanism for l-butylphthalide would not make the claims patentable over the prior art because the reduction in the volume of the cerebral infarct is deemed by the Examiner "to be a necessary consequence of what is deliberately intended in the prior art method." Applicants disagree. As explained above, there is no clear relationship between the changes in apoptosis or mitochondrial membrane fluidity or electron microscopic changes of the mitochondria and the volume of cerebral infarct. Contrary to the assertion of the Office Action, the reduction in the volume of the cerebral infarct is NOT "a necessary consequence of what is deliberately intended in the prior art method."

At least based on the above reasons, the obviousness rejections of claims 6-8 over Chang in view of Xiong and Izozumi should be withdrawn.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The Office is hereby authorized to charge any fees in relation to this paper under 37 C.F.R. 1.16 and 1.17 to the Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

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